PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

LICATA, Jane, Massey
Law Offices of Jane Massey Licata
66 E. Main Street
Marlton, NJ 08053
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 10 April 2000 (10.04.00)	
Applicant's or agent's file reference RTSP-0041	**IMPORTANT NOTIFICATION**
International application No. PCT/US00/00525	International filing date (day/month/year) 06 January 2000 (06.01.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 19 July 1999 (19.07.99)
Applicant ISIS PHARMACEUTICALS, INC. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
19 July 1999 (19.07.99)	09/357,070	US	20 Marc 2000 (20.03.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.36

Authorized officer

Taïeb Akremi

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON NJ 08053

Docket System ✓
Status Report ✓
Docket Book ✓
8/13/01 WO

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	13 JUN 2001
Applicant's or agent's file reference: RTSP-0041	REPLY DUE within TWO months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/00525	06 JANUARY 2000	19 JULY 1999

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant
ISIS PHARMACEUTICALS, INC.

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request the Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 19 NOVEMBER 2001

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	JOHN LEGUYADER
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/408 (cover sheet) (July 1998) ★

PATENT COOPERATION ATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON NJ 08053

Docket System _____
Status Report _____
Docket Book _____

WRITTEN OPINION

(PCT Rule 66)

	Date of Mailing *(day/month/year)*
Applicant's or agent's file reference RTSP-0041	REPLY DUE within TWO months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/00525	06 JANUARY 2000	19 JULY 1999

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant
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- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

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When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 19 NOVEMBER 2001.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JOHN LEGUYADER
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/408 (cover sheet) (July 1998) ★

WRITTEN OPINION

International application No.
PCT/US00/00525

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

[ ] the international application as originally filed

[X] the description:
pages 1-81 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 82-83 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

WRITTEN OPINION

International application No.
PCT/US00/00525

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	3-4, 16-19	YES
	Claims	1-2, 5-15	NO
Inventive Step (IS)	Claims	3-4, 16-19	YES
	Claims	1-2, 5-15	NO
Industrial Applicability (IA)	Claims	1-19	YES
	Claims	NONE	NO

2. citations and explanations

Claims 1-2 and 5-15 lack an inventive step under PCT Article 33(3) as being obvious over Dhand et al. or Chantry et al. in view of Baracchini et al.

Claims 1-2 and 5-15 are drawn to antisense compounds targeted to a nucleic acid molecule encoding human PI3 kinase p110 delta, having modified internucleoside linkages, and methods of inhibiting the expression of PI3 kinase p110 delta in human cells or tissues with said antisense oligonucleotides.

Dhand et al. and Chantry et al. teach inhibition of the human p110 PI3 kinase delta isoform. Dhand et al. teach sequence specific mutation of the p110 PI3 delta gene (see Example 11, col. 16) to inhibit binding of p110 to the p85 subunit. Chantry et al. teach general design of modulators or inhibitors of p110 binding to p85 (see '753, cols. 3-4) and prophetic construction of a p110 PI3 kinase delta knock-out mouse (see '753, example 8, col. 12). Neither specifically teach antisense inhibition to the p110 PI3 kinase delta isoform.

Baracchini et al. teach design of antisense oligonucleotides to a known gene, and modifications (see columns 5-9) to optimize an antisense oligonucleotide for improved function.

It would have been obvious to design an antisense oligonucleotide to the human p110 PI3 kinase delta gene since Dhand et al. and Chantry et al. teach motivation to inhibit the human p110 PI3 kinase delta gene and since it was well known in the art to design antisense to a known gene target as taught by Baracchini et al. One would further have been motivated to administer said antisense to cells in culture as taught by Baracchini et al.

Claims 3-4 and 16-19 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the specific SEQ ID NOs claimed nor in vivo administration of antisense to cells in whole organisms.

---------- NEW CITATIONS ----------

US 5,801,154 A (BARACCHINI ET AL) 01 September 1998 (01/09/98), see entire document, especially columns 7-9.

(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

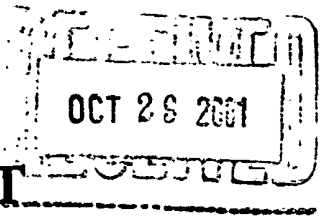
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12N 15/00, 15/11; C12Q 1/68; A61K 48/00 and US Cl.: 435/6, 366, 375, 91.1; 536/23.1, 24.3, 24.5; 514/44

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

US 5,741,689 A (DHAND ET AL) 21 April 1998 (21/04/98), see entire document, especially abstract.

US 5,882,910 A (CHANTRY ET AL) 16 March 1999 (16/03/99), see entire document, expecially abstract.

PATENT COOPERATION TREATY



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON NJ 08053

Docket System ✓
Status Report ✓
Docket Book ✓
NP= 1/19/02

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	26 OCT 2001
Applicant's or agent's file reference: RTSP-0041	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US00/00525	06 JANUARY 2000	19 JULY 1999

Applicant: ISIS PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	MARY SCHMIDT
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992)★

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RTSP-0041	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/00525	International filing date *(day/month/year)* 06 JANUARY 2000	Priority date *(day/month/year)* 19 JULY 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant ISIS PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12 FEBRUARY 2001	30 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MARY SCHMIDT Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

[redacted]ional application No.
PCT/US00/00525

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-81 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:
pages 82-83 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

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☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

[redacted]ional application No.
PCT/US00/00525

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	3-4, 16-19	YES
	Claims	1-2, 5-15	NO
Inventive Step (IS)	Claims	3-4, 16-19	YES
	Claims	1-2, 5-15	NO
Industrial Applicability (IA)	Claims	1-19	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-2 and 5-15 lack an inventive step under PCT Article 33(3) as being obvious over Dhand et al. or Chantry et al. in view of Baracchini et al.

Claims 1-2 and 5-15 are drawn to antisense compounds targeted to a nucleic acid molecule encoding human PI3 kinase p110 delta, having modified internucleoside linkages, and methods of inhibiting the expression of PI3 kinase p110 delta in human cells or tissues with said antisense oligonucleotides.

Dhand et al. and Chantry et al. teach inhibition of the human p110 PI3 kinase delta isoform. Dhand et al. teach sequence specific mutation of the p110 PI3 delta gene (see Example 11, col. 16) to inhibit binding of p110 to the p85 subunit. Chantry et al. teach general design of modulators or inhibitors of p110 binding to p85 (see '753, cols. 3-4) and prophetic construction of a p110 PI3 kinase delta knock-out mouse (see '753, example 8, col. 12). Neither specifically teach antisense inhibition to the p110 PI3 kinase delta isoform.

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(Continued on Supplemental Sheet.)

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Continuation of: Boxes I - VIII

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